

**PCT****REQUEST**

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference  
(if desired) (12 characters maximum) PTS-0055WO
**Box No. I TITLE OF INVENTION**  
**ANTISENSE MODULATION OF EXTRACELLULAR-SIGNAL-REGULATED KINASE-6 EXPRESSION**
**Box No. II APPLICANT**  This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

**ISIS Pharmaceuticals Inc.**  
2292 Faraday Avenue  
Carlsbad, California 92008 US

Telephone No.  
760-603-2385Facsimile No.  
760-603-3820

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality:  
USState (that is, country) of residence:  
US

This person is applicant  all designated States  all designated States except the United States of America  the United States of America only  the States indicated in the Supplemental Box for the purposes of:

**Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

**Marcusson, Eric G.**  
6369 Caminito de Pastel  
San Diego, California 92111 US

This person is:

 applicant only applicant and inventor inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:  
USState (that is, country) of residence:  
US

This person is applicant  all designated States  all designated States except the United States of America  the United States of America only  the States indicated in the Supplemental Box for the purposes of:

 Further applicants and/or (further) inventors are indicated on a continuation sheet.**Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

 agent common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

**Bak, Mary E.**  
Howson and Howson  
Spring House Corporate Center  
P.O. Box 457  
Spring House, Pennsylvania 19477 US

Telephone No.

215-540-9200

Facsimile No.

215-540-5818

Teleprinter No.

Agent's registration No. with the Office  
31,215

Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

## Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

*If none of the following sub-boxes is used, this sheet should not be included in the request.*

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Bennett, C. Frank  
1347 Cassins Street  
Carlsbad, California 92009 US

This person is:

- applicant only  
 applicant and inventor  
 inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:  
USState (that is, country) of residence:  
US

This person is applicant for the purposes of:  all designated States  all designated States except the United States of America  the United States of America only  the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Dobie, Kenneth W.  
703 Stratford Ct., #4  
Del Mar, California 92014 US

This person is:

- applicant only  
 applicant and inventor  
 inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:  
UKState (that is, country) of residence:  
US

This person is applicant for the purposes of:  all designated States  all designated States except the United States of America  the United States of America only  the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- applicant only  
 applicant and inventor  
 inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:  all designated States  all designated States except the United States of America  the United States of America only  the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- applicant only  
 applicant and inventor  
 inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:  all designated States  all designated States except the United States of America  the United States of America only  the States indicated in the Supplemental Box

Further applicants and/or (further) inventors are indicated on another continuation sheet.

## Box No. V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

## Regional Patent

- AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (*if other kind of protection or treatment desired, specify on dotted line*) .....
- EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT .....
- EP European Patent: AT Austria, BE Belgium, BG Bulgaria, CH & LI Switzerland and Liechtenstein, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, SI Slovenia, SK Slovakia, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT .....
- OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (*if other kind of protection or treatment desired, specify on dotted line*) .....

National Patent (*if other kind of protection or treatment desired, specify on dotted line*):

- |   |  |   |
|---|--|---|
| <input checked="" type="checkbox"/> AE United Arab Emirates .....               | <input checked="" type="checkbox"/> GM Gambia .....                                    | <input checked="" type="checkbox"/> NZ New Zealand .....                      |
| <input checked="" type="checkbox"/> AG Antigua and Barbuda .....                | <input checked="" type="checkbox"/> HR Croatia .....                                   | <input checked="" type="checkbox"/> OM Oman .....                             |
| <input checked="" type="checkbox"/> AL Albania .....                            | <input checked="" type="checkbox"/> HU Hungary .....                                   | <input checked="" type="checkbox"/> PH Philippines .....                      |
| <input checked="" type="checkbox"/> AM Armenia .....                            | <input checked="" type="checkbox"/> ID Indonesia .....                                 | <input checked="" type="checkbox"/> PL Poland .....                           |
| <input checked="" type="checkbox"/> AT Austria .....                            | <input checked="" type="checkbox"/> IL Israel .....                                    | <input checked="" type="checkbox"/> PT Portugal .....                         |
| <input checked="" type="checkbox"/> AU Australia .....                          | <input checked="" type="checkbox"/> IN India .....                                     | <input checked="" type="checkbox"/> RO Romania .....                          |
| <input checked="" type="checkbox"/> AZ Azerbaijan .....                         | <input checked="" type="checkbox"/> IS Iceland .....                                   | <input checked="" type="checkbox"/> RU Russian Federation .....               |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina .....             | <input checked="" type="checkbox"/> JP Japan .....                                     |   |
| <input checked="" type="checkbox"/> BB Barbados .....                           | <input checked="" type="checkbox"/> KE Kenya .....                                     | <input checked="" type="checkbox"/> SC Seychelles .....                       |
| <input checked="" type="checkbox"/> BG Bulgaria .....                           | <input checked="" type="checkbox"/> KG Kyrgyzstan .....                                | <input checked="" type="checkbox"/> SD Sudan .....                            |
| <input checked="" type="checkbox"/> BR Brazil .....                             | <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea .....     | <input checked="" type="checkbox"/> SE Sweden .....                           |
| <input checked="" type="checkbox"/> BY Belarus .....                            | <input checked="" type="checkbox"/> KR Republic of Korea .....                         | <input checked="" type="checkbox"/> SG Singapore .....                        |
| <input checked="" type="checkbox"/> BZ Belize .....                             | <input checked="" type="checkbox"/> KZ Kazakhstan .....                                | <input checked="" type="checkbox"/> SK Slovakia .....                         |
| <input checked="" type="checkbox"/> CA Canada .....                             | <input checked="" type="checkbox"/> LC Saint Lucia .....                               | <input checked="" type="checkbox"/> SL Sierra Leone .....                     |
| <input checked="" type="checkbox"/> CH & LI Switzerland and Liechtenstein ..... | <input checked="" type="checkbox"/> LK Sri Lanka .....                                 | <input checked="" type="checkbox"/> TJ Tajikistan .....                       |
| <input checked="" type="checkbox"/> CN China .....                              | <input checked="" type="checkbox"/> LR Liberia .....                                   | <input checked="" type="checkbox"/> TM Turkmenistan .....                     |
| <input checked="" type="checkbox"/> CO Colombia .....                           | <input checked="" type="checkbox"/> LS Lesotho .....                                   | <input checked="" type="checkbox"/> TN Tunisia .....                          |
| <input checked="" type="checkbox"/> CR Costa Rica .....                         | <input checked="" type="checkbox"/> LT Lithuania .....                                 | <input checked="" type="checkbox"/> TR Turkey .....                           |
| <input checked="" type="checkbox"/> CU Cuba .....                               | <input checked="" type="checkbox"/> LU Luxembourg .....                                | <input checked="" type="checkbox"/> TT Trinidad and Tobago .....              |
| <input checked="" type="checkbox"/> CZ Czech Republic .....                     | <input checked="" type="checkbox"/> LV Latvia .....                                    | <input checked="" type="checkbox"/> TZ United Republic of Tanzania .....      |
| <input checked="" type="checkbox"/> DE Germany .....                            | <input checked="" type="checkbox"/> MA Morocco .....                                   | <input checked="" type="checkbox"/> UA Ukraine .....                          |
| <input checked="" type="checkbox"/> DK Denmark .....                            | <input checked="" type="checkbox"/> MD Republic of Moldova .....                       | <input checked="" type="checkbox"/> UG Uganda .....                           |
| <input checked="" type="checkbox"/> DM Dominica .....                           | <input checked="" type="checkbox"/> MG Madagascar .....                                | <input checked="" type="checkbox"/> US United States of America .....         |
| <input checked="" type="checkbox"/> DZ Algeria .....                            | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia ..... | <input checked="" type="checkbox"/> continuation .....                        |
| <input checked="" type="checkbox"/> EC Ecuador .....                            | <input checked="" type="checkbox"/> MN Mongolia .....                                  | <input checked="" type="checkbox"/> UZ Uzbekistan .....                       |
| <input checked="" type="checkbox"/> EE Estonia .....                            | <input checked="" type="checkbox"/> MW Malawi .....                                    | <input checked="" type="checkbox"/> VC Saint Vincent and the Grenadines ..... |
| <input checked="" type="checkbox"/> ES Spain .....                              | <input checked="" type="checkbox"/> MX Mexico .....                                    | <input checked="" type="checkbox"/> VN Viet Nam .....                         |
| <input checked="" type="checkbox"/> FI Finland .....                            | <input checked="" type="checkbox"/> MZ Mozambique .....                                | <input checked="" type="checkbox"/> YU Yugoslavia .....                       |
| <input checked="" type="checkbox"/> GB United Kingdom .....                     | <input checked="" type="checkbox"/> NO Norway .....                                    | <input checked="" type="checkbox"/> ZA South Africa .....                     |
| <input checked="" type="checkbox"/> GD Grenada .....                            |  | <input checked="" type="checkbox"/> ZM Zambia .....                           |
| <input checked="" type="checkbox"/> GE Georgia .....                            |  | <input checked="" type="checkbox"/> ZW Zimbabwe .....                         |
| <input checked="" type="checkbox"/> GH Ghana .....                              |  |   |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- NI Nicaragua .....
- PG Papua New Guinea .....
- 
- SY Syrian Arab Republic .....
- 

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (*Confirmation (including fees) must reach the receiving Office within the 15-month time limit.*)

**Supplemental Box***If the Supplemental Box is not used, this sheet should not be included in the request.*

1. *If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No...." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*
  - (i) *if more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*
  - (ii) *if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*
  - (iii) *if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*
  - (iv) *if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*
  - (v) *if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*
  - (vi) *if, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*
2. *If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

**"Continuation of Box No. IV"**

Stanley B. Kita, Reg. No. 24,561  
 George A. Smith, Jr., Reg. No. 24,442  
 Cathy A. Kodroff, Reg. 33,980  
 William Bak, Reg. No. 37,277  
 Tracy U. Palovich, Reg. No. 47,840 (patent agent)

Above attorneys are members of the firm of  
 Howson and Howson  
 Spring House Corporate Center  
 P.O. Box 457  
 Spring House, Pennsylvania 19477 US

Herb Boswell, Reg. No. 27,311  
 Laurel S. Bernstein, Reg. No. 37,280  
 Neil S. Bartfeld, Reg. No. 39,901  
 Matthew Grumpling, Reg. No. 44,427  
 Donna T. Ward, Reg. No. 48,271

of ISIS Pharmaceuticals Inc.  
 2292 Faraday Avenue  
 Carlsbad, California 92008 US

**"Continuation of Box No. V"**  
 United States  
 USSN 10/174,465  
 filed: 17 June 2002

USSN 10/348,431  
 filed: 17 January 2003

Box No. VI PRIORITY CLAIM				
The priority of the following earlier application(s) is hereby claimed:				
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:*	international application: receiving Office
item (1) 17 June 2002	10/174,465	US		
item (2) 17 January 2003	10/348,431	US		
item (3)				
item (4)				
item (5)				
<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.				
The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) ( <i>only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office</i> ) identified above as:				
<input checked="" type="checkbox"/> all items <input type="checkbox"/> item (1) <input type="checkbox"/> item (2) <input type="checkbox"/> item (3) <input type="checkbox"/> item (4) <input type="checkbox"/> item (5) <input type="checkbox"/> other, see Supplemental Box				
* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):				
Box No. VII INTERNATIONAL SEARCHING AUTHORITY				
Choice of International Searching Authority (ISA) ( <i>if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used</i> ):				
ISA / US				
Request to use results of earlier search; reference to that search ( <i>if an earlier search has been carried out by or requested from the International Searching Authority</i> ):				
Date (day/month/year)	Number	Country (or regional Office)		
Box No. VIII DECLARATIONS				
The following declarations are contained in Boxes Nos. VIII (i) to (v) ( <i>mark the applicable check-boxes below and indicate in the right column the number of each type of declaration</i> ):				Number of declarations
<input type="checkbox"/> Box No. VIII (i)	Declaration as to the identity of the inventor			:
<input type="checkbox"/> Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent			:
<input type="checkbox"/> Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application			:
<input type="checkbox"/> Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)			:
<input type="checkbox"/> Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty			:

**Box No. IX CHECK LIST; LANGUAGE OF FILING**

This international application contains:		This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):		Number of items
(a) In paper form, the following number of sheets :		1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input type="checkbox"/> original separate power of attorney 3. <input type="checkbox"/> original general power of attorney 4. <input checked="" type="checkbox"/> copy of general power of attorney; reference number, if any: ..... 5. <input type="checkbox"/> statement explaining lack of signature 6. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): ..... 7. <input type="checkbox"/> translation of international application into (language): ..... 8. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 9. <input checked="" type="checkbox"/> sequence listings in computer readable form (indicate type and number of carriers)		
request (including declaration sheets)	: 6			1
description (excluding sequence listings and/or tables related thereto)	: 127			
claims	: 9			
abstract	: 1			
drawings	: .....			
<b>Sub-total number of sheets</b>	<b>: 143</b>			
sequence listings	: 88			
tables related thereto	: .....			
<i>(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)</i>				
<b>Total number of sheets</b>	<b>: 231</b>			
(b) <input type="checkbox"/> only in computer readable form (Section 801(a)(i))		10. <input type="checkbox"/> tables in computer readable form related to sequence listings (indicate type and number of carriers)		1
(i) <input type="checkbox"/> sequence listings		(i) <input type="checkbox"/> copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)		
(ii) <input type="checkbox"/> tables related thereto		(ii) <input type="checkbox"/> (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter		
(c) <input checked="" type="checkbox"/> also in computer readable form (Section 801(a)(ii))		(iii) <input checked="" type="checkbox"/> together with relevant statement as to the identity of the copy or copies with the sequence listings mentioned in left column		
(i) <input checked="" type="checkbox"/> sequence listings		(i) <input type="checkbox"/> copy submitted for the purposes of international search under Section 802(b-quarter) only (and not as part of the international application)		
(ii) <input type="checkbox"/> tables related thereto		(ii) <input type="checkbox"/> (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quarter)		
Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the		(iii) <input type="checkbox"/> together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column		
<input checked="" type="checkbox"/> sequence listings: 1. diskette .....		11. <input checked="" type="checkbox"/> other (specify): ..transmittal letter to the USRO.....		1
<input type="checkbox"/> tables related thereto: .....				
<i>(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)</i>				

Figure of the drawings which should accompany the abstract: Language of filing of the international application: English

**Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE**  
*Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).*

By: Mary E. Bak  
 Mary E. Bak  
 Attorney for Applicants

For receiving Office use only	
1. Date of actual receipt of the purported international application:	
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	
6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid	
For International Bureau use only	
2. Drawings: <input type="checkbox"/> received:  <input type="checkbox"/> not received:	

Date of receipt of the record copy by the International Bureau: